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EXAMINER	
WOOLWINE, SAMUEL C	
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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,840	DRESSMAN ET AL.	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39,43,45,60,62 and 91-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,43,45,60,62 and 91-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37, 43, 45, 60, 91, 92 and 95-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holliger et al (WO 02/22869, prior art of record) in view of Vogelstein et al (PNAS 96:9236-9241, August 1999, prior art of record) and Paulsen et al (WO 89/11546).

With regard to claims 37, 43, 45, 60 and 91, Holliger taught (paragraph spanning pages 76-77):

Example 25: Method for the parallel genotyping of heterogenous populations of cells.

The approach involves compartmentation of the cells in question in the emulsion (see WO9303151) together with PCR reagents etc. and polymerase. However, instead of linking genes derived from one cell by PCR assembly, one (or several) biotinylated primers are used as well as a streptavidin coated polystyrene beads (or any other suitable means of linking primers onto beads). Thus, PCR fragments from one single cell are transferred to a single bead. Beads are pooled, interrogated for presence of a certain mutation or allele using fluorescently labelled probes (as described for "Digital PCR") and counted by FACS. Multiplex PCR allows the simultaneous interrogation of 10 or maybe more markers. Single beads can also be sorted for sequencing.

One of ordinary skill would infer from this passage: (1) forming an emulsion with cells (each of which comprises "one or more species of analyte DNA molecules"), PCR reagents and beads (which beads are either already bound to primers or become bound to primers within the emulsion droplets), (2) carrying out the PCR reaction to produce beads bound to PCR fragments, each bead being bound to PCR products derived from a single cell, and (3) interrogating the beads with labeled probes and analyzing by flow cytometry, i.e. FACS (thereby determining a sequence feature, based on the labeled probe). Also the passage states that "one (or several) biotinylated primers are used", in which case, if only one biotinylated primer were used, then each bead (after the PCR) would be "bound to a plurality of copies of one species of analyte DNA molecule".

With regard to claim 60, Holliger taught that single beads could also be sorted for sequencing. Hence, it would have been obvious to "isolate using fluorescence activated cell sorting product beads which are bound to a plurality of copies of a first species of

analyte DNA molecule from product beads which are bound to a plurality copies of a second species of analyte DNA molecule" for the purpose of sequencing.

Holliger did not teach "separating product beads from analyte DNA molecules which are not bound to product beads" as recited in claims 37, 43, 45, 60 and 91.

Holliger also did not teach hybridization to oligonucleotide probes which are differentially labeled, as recited in claim 43; determining an amount of beads comprising a first species of analyte DNA as a fraction of product beads, as recited in claim 45; or expressly teach that the fluorescently labeled probes were "oligonucleotides", as recited in claims 91 and 92 (though one of skill in the art would have assumed this, given that Holliger stated the purpose of the probes was to interrogate for presence of certain mutations or alleles). Holliger also did not teach the label was fluorescein as recited in claim 95; biotin-conjugated oligonucleotide probe as recited in claim 96, or that the probes had a stem and loop structure as recited in claims 97 and 98. However, Holliger expressly stated the fluorescently labeled probes were "as described for 'Digital PCR' ".

Vogelstein presented the seminal disclosure of "Digital PCR". With regard to claims 43, 91 and 92 Vogelstein determined the presence of certain alleles or mutations using differentially labeled oligonucleotide probes (see figure 1: MB-Red and MB-Green; see also page 9237, column 1, "Oligonucleotides and DNA Sequencing"). With regard to claim 95, Vogelstein taught fluorescein (page 9237, column 1, "Oligonucleotides and DNA Sequencing"). With regard to claims 97 and 98, Vogelstein taught probes with stem and loop structure (see figure 1).

With regard to claim 45, Vogelstein taught (abstract, emphasis provided): "The process provides a reliable and quantitative measure of the proportion of variant sequences within a DNA sample." Hence, it would have been obvious to determine "an amount of product beads comprising a first species of analyte DNA molecule as a fraction of product beads" in order to determine the proportion of variant sequences within the sample, as suggested by Vogelstein.

With regard to claims 37, 43, 45, 60 and 91, Paulsen taught a method comprising amplifying DNA in the presence of magnetic beads attached to primers (i.e. one primer of the pair used for PCR was attached to the beads, the other primer in solution), followed by removal (separation) of the strands of the PCR product that were not bound to the beads, and detection of the amplified DNA (e.g. page 2, lines 23-35):

According to the present invention a method for gene assay in a test medium is thus provided, and said method is characterized by

a) denaturing DNA in the test medium,

b) contacting the test medium under hybridizing conditions with heat-resistant DNA-polymerase, deoxynucleotides, two different oligonucleotide primers, one of which is soluble, whereas the other is bonded to superparamagnetic particles,

c) amplification of DNA,

d) removal of the DNA strand which is not connected with the particles, as well as free oligonucleide primers,

e) detecting amplified material.

Paulsen taught that the amplified material could be detected by specific probing with oligonucleotides (page 3, lines 24-26). With regard to claim 60, Paulsen taught biotinylated oligonucleotide probes that could be subsequently detected by adding avidine- or streptavidine-conjugated enzymes, fluorochromes, etc (page 4, lines 1-11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Holliger by using magnetic beads, and separating the strand of the PCR product bound to the beads from the complementary strand of the PCR product not bound to the beads as disclosed by Paulsen. In order to interrogate with mutation- or allele-specific probes as disclosed by Holliger, it would have been necessary to remove the complementary strand of the PCR product, so that the probe would be permitted to anneal to the remaining strand bound to the beads. By using the magnetic beads as disclosed by Paulsen, washing, probing and detection could be carried out readily, efficiently, and very quickly by use of a magnet, which would permit complete automation of the entire assay (page 6, lines 12-16).

Moreover, it would have been obvious to use the probing strategy taught by Vogelstein for Digital PCR, since Holliger expressly directed one to use fluorescently labeled probes "as described for 'Digital PCR' " (hence meeting the limitations of claims 37, 43, 45, 60, 91, 92, 95, 97 and 98). Finally, it would have been obvious to substitute probes directly labeled with fluorochromes (as disclosed by Vogelstein), with probes coupled to biotin for indirect detection by avidine-conjugated labels as disclosed by Paulsen (hence meeting the limitations of claim 96), since this was an art-recognized

alternative manner for detecting a nucleic acid sequence using sequence-specific oligonucleotide probes (MPEP 2144.06).

Claims 91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holliger et al (WO 02/22869, prior art of record) in view of Paulsen et al (WO 89/11546) and Cohen et al (US 2006/0234221, prior art of record).

With regard to claim 91, Holliger taught (paragraph spanning pages 76-77):

> Example 25: Method for the parallel genotyping of heterogenous populations of cells.
>
> The approach involves compartmentation of the cells in question in the emulsion (see WO9303151) together with PCR reagents etc. and polymerase. However, instead of linking genes derived from one cell by PCR assembly, one (or several) biotinylated primers are used as well as a streptavidin coated polystyrene beads (or any other suitable means of linking primers onto beads). Thus, PCR fragments from one single cell are transferred to a single bead. Beads are pooled, interrogated for presence of a certain mutation or allele using fluorescently labelled probes (as described for "Digital PCR") and counted by FACS. Multiplex PCR allows the simultaneous interrogation of 10 or maybe more markers. Single beads can also be sorted for sequencing.

One of ordinary skill would infer from this passage: (1) forming an emulsion with cells (each of which comprises "one or more species of analyte DNA molecules"), PCR reagents and beads (which beads are either already bound to primers or become bound to primers within the emulsion droplets), (2) carrying out the PCR reaction to produce beads bound to PCR fragments, each bead being bound to PCR products derived from a single cell, and (3) interrogating the beads with labeled probes and analyzing by flow cytometry, i.e. FACS (thereby determining a sequence feature, based on the labeled

probe). Also the passage states that "one (or several) biotinylated primers are used", in which case, if only one biotinylated primer were used, then each bead (after the PCR) would be "bound to a plurality of copies of one species of analyte DNA molecule". One of ordinary skill would also have noted that Holliger taught the beads could be further sorted for sequencing.

Holliger did not teach "separating product beads from analyte DNA molecules which are not bound to product beads" as recited in claim 91 or determining a sequence feature by allele specific priming as recited in claims 91 and 93.

With regard to claim 91, Paulsen taught a method comprising amplifying DNA in the presence of magnetic beads attached to primers (i.e. one primer of the pair used for PCR was attached to the beads, the other primer in solution), followed by removal (separation) of the strands of the PCR product that were not bound to the beads, and detection of the amplified DNA (e.g. page 2, lines 23-35):

According to the present invention a method for gene assay in a test medium is thus provided, and said method is characterized by

a) denaturing DNA in the test medium,

b) contacting the test medium under hybridizing conditions with heat-resistant DNA-polymerase, deoxynucleotides, two different oligonucleotide primers, one of which is soluble, whereas the other is bonded to superparamagnetic particles,

c) amplification of DNA,

d) removal of the DNA strand which is not connected with the particles, as well as free oligonucleide primers,

e) detecting amplified material.

Cohen taught (paragraph [0097]):

"Allele specific primers may be designed such that a biallelic marker or other polymorphism of the invention is at the 3' end of the contiguous span and the contiguous span is present at the 3' end of the primer. Such allele specific primers tend to selectively prime an amplification or sequencing reaction so long as they are used with a nucleic acid sample that contains one of the two alleles present at said marker."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform allele specific priming for the sequencing reactions on the sorted beads described by Holliger (i.e. "beads can also be sorted for sequencing"), since Cohen demonstrates that allele-specific priming was a conventional technique known in the art for priming a sequencing reaction, and was certainly a known method of determining a "sequence feature".

It would also have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Holliger by using magnetic beads, and separating the strand of the PCR product bound to the beads from the complementary strand of the PCR product not bound to the beads as disclosed by Paulsen. In order to anneal an allele-specific primer (or any primer for that matter) to the strand of the PCR product directly attached to the bead, it would have been necessary to remove the complementary strand of the PCR product, so that the primer would be permitted to anneal to the remaining strand bound to the beads. By using the magnetic beads as disclosed by Paulsen, washing, probing and detection could be carried out readily, efficiently, and very quickly by use of a magnet, which would permit complete automation of the entire assay (page 6, lines 12-16).

Claims 91 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holliger et al (WO 02/22869, prior art of record) in view of Paulsen et al (WO 89/11546) and Nikiforov et al (Nucleic Acids Research 22(20):4167-4175, 1994, prior art of record).

With regard to claim 91, Holliger taught (paragraph spanning pages 76-77):

Example 25: Method for the parallel genotyping of heterogenous populations of cells.

The approach involves compartmentation of the cells in question in the emulsion (see WO9303151) together with PCR reagents etc. and polymerase. However, instead of linking genes derived from one cell by PCR assembly, one (or several) biotinylated primers are used as well as a streptavidin coated polystyrene beads (or any other suitable means of linking primers onto beads). Thus, PCR fragments from one single cell are transferred to a single bead. Beads are pooled, interrogated for presence of a certain mutation or allele using fluorescently labelled probes (as described for "Digital PCR") and counted by FACS. Multiplex PCR allows the simultaneous interrogation of 10 or maybe more markers. Single beads can also be sorted for sequencing.

One of ordinary skill would infer from this passage: (1) forming an emulsion with cells (each of which comprises "one or more species of analyte DNA molecules"), PCR reagents and beads (which beads are either already bound to primers or become bound to primers within the emulsion droplets), (2) carrying out the PCR reaction to produce beads bound to PCR fragments, each bead being bound to PCR products derived from a single cell, and (3) interrogating the beads with labeled probes and analyzing by flow cytometry, i.e. FACS (thereby determining a sequence feature, based on the labeled probe). Also the passage states that "one (or several) biotinylated primers are used", in which case, if only one biotinylated primer were used, then each bead (after the PCR) would be "bound to a plurality of copies of one species of analyte DNA molecule". One of ordinary skill would also have noted that Holliger taught the beads could be further sorted for sequencing.

Holliger did not teach "separating product beads from analyte DNA molecules which are not bound to product beads" as recited in claim 91 or determining a sequence feature by single nucleotide extension as recited in claims 91 and 94.

With regard to claim 91, Paulsen taught a method comprising amplifying DNA in the presence of magnetic beads attached to primers (i.e. one primer of the pair used for PCR was attached to the beads, the other primer in solution), followed by removal (separation) of the strands of the PCR product that were not bound to the beads, and detection of the amplified DNA (e.g. page 2, lines 23-35):

> According to the present invention a method for gene assay in a test medium is thus provided, and said method is characterized by
> a) denaturing DNA in the test medium,
> b) contacting the test medium under hybridizing conditions with heat-resistant DNA-polymerase, deoxynucleotides, two different oligonucleotide primers, one of which is soluble, whereas the other is bonded to superparamagnetic particles,
> c) amplification of DNA,
> d) removal of the DNA strand which is not connected with the particles, as well as free oligonucleide primers,
> e) detecting amplified material.

Nikiforov taught a method of sequencing in which a primer was annealed to a template and then extended with a single, labeled nucleotide to determine a sequence feature (i.e. a single nucleotide polymorphism); see figure 1, steps 3-5.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform single nucleotide extension for the sequencing reactions on the sorted beads described by Holliger (i.e. "beads can also be sorted for sequencing"), since Nikiforov demonstrates that single nucleotide extension was a conventional technique known in the art for analyzing nucleic acid, and in particular for determining a "sequence feature".

It would also have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Holliger by using magnetic beads, and separating the strand of the PCR product bound to the beads from the complementary strand of the PCR product not bound to the beads as disclosed by Paulsen. In order to anneal a primer for single nucleotide extension to the strand of the PCR product directly attached to the bead, it would have been necessary to remove the complementary strand of the PCR product, so that the primer would be permitted to anneal to the remaining strand bound to the beads. By using the magnetic beads as disclosed by Paulsen, washing, probing and detection could be carried out readily, efficiently, and very quickly by use of a magnet, which would permit complete automation of the entire assay (page 6, lines 12-16).

Claims 39 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holliger et al (WO 02/22869, prior art of record) in view of Paulsen et al (WO 89/11546) and Chang et al (US 6,403,037).

With regard to claims 39 and 62, Holliger taught (paragraph spanning pages 76-77):

> Example 25: Method for the parallel genotyping of heterogenous populations of cells.
>
> The approach involves compartmentation of the cells in question in the emulsion (see WO9303151) together with PCR reagents etc. and polymerase. However, instead of linking genes derived from one cell by PCR assembly, one (or several) biotinylated primers are used as well as a streptavidin coated polystyrene beads (or any other suitable means of linking primers onto beads). Thus, PCR fragments from one single cell are transferred to a single bead. Beads are pooled, interrogated for presence of a certain mutation or allele using fluorescently labelled probes (as described for "Digital PCR") and counted by FACS. Multiplex PCR allows the simultaneous interrogation of 10 or maybe more markers. Single beads can also be sorted for sequencing.

One of ordinary skill would infer from this passage: (1) forming an emulsion with cells (each of which comprises "one or more species of analyte DNA molecules"), PCR reagents and beads (which beads are either already bound to primers or become bound to primers within the emulsion droplets), (2) carrying out the PCR reaction to produce beads bound to PCR fragments, each bead being bound to PCR products derived from a single cell, and (3) interrogating the beads with labeled probes and analyzing by flow cytometry, i.e. FACS (thereby determining a sequence feature, based on the labeled probe). Also the passage states that "one (or several) biotinylated primers are used", in which case, if only one biotinylated primer were used, then each bead (after the PCR) would be "bound to a plurality of copies of one species of analyte DNA molecule". One of ordinary skill would also have noted that Holliger taught the beads could be further sorted for sequencing.

Holliger did not teach "separating product beads from analyte DNA molecules which are not bound to product beads" as recited in claims 39 and 62. Holliger did teach that single beads could be sorted for sequencing (hence, isolating product beads bound to a first species of analyte DNA as recited in claim 39, which would also isolate said product beads from beads having a second species of analyte DNA as recited in claim 62). However, Holliger did not teach amplifying the first species of DNA from the isolated product beads (as recited in claims 39 and 62).

With regard to claims 39 and 62, Paulsen taught a method comprising amplifying DNA in the presence of magnetic beads attached to primers (i.e. one primer of the pair used for PCR was attached to the beads, the other primer in solution), followed by removal (separation) of the strands of the PCR product that were not bound to the beads, and detection of the amplified DNA (e.g. page 2, lines 23-35):

> According to the present invention a method for gene assay in a test medium is thus provided, and said method is characterized by
> a) denaturing DNA in the test medium,
> b) contacting the test medium under hybridizing conditions with heat-resistant DNA-polymerase, deoxynucleotides, two different oligonucleotide primers, one of which is soluble, whereas the other is bonded to superparamagnetic particles,
> c) amplification of DNA,
> d) removal of the DNA strand which is not connected with the particles, as well as free oligonucleide primers,
> e) detecting amplified material.

Chang taught (column 1, lines 57-65, emphasis added):

"Polynucleotide amplification assays can be used in a wide range of applications such as the generation of specific sequences of cloned double-stranded DNA for use as probes, the generation of probes specific for uncloned genes by selective amplification of particular segments of cDNA, the generation of libraries of cDNA from small amounts of mRNA, the generation of large amounts of DNA for sequencing and the analysis of mutations."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Holliger by using magnetic beads, and separating the strand of the PCR product bound to the beads from the complementary strand of the PCR product not bound to the beads as disclosed by Paulsen. In order to interrogate with mutation- or allele-specific probes as disclosed by Holliger, it would have been necessary to remove the complementary strand of the PCR product, so that the probe would be permitted to anneal to the remaining strand bound to the beads. By using the magnetic beads as disclosed by Paulsen, washing, probing and detection could be carried out readily, efficiently, and very quickly by use of a magnet, which would permit complete automation of the entire assay (page 6, lines 12-16).

It would also have been *prima facie* obvious to one of ordinary skill in the art to amplify the DNA from the sorted beads (e.g. where Holliger states: "beads can also be sorted for sequencing"), since it was known in the art to amplify nucleic acid prior to

conducting sequencing reactions in order to provide large amounts of DNA to work with, as disclosed by Chang.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Primary Examiner